
PATHOLOGICAL DEMONSTRATIONS

by

DR. C. C. LUSHBAUGH
Instructor of Pathology, University of Chicago

I think that it probably would be more interesting to all of you if you saw the pathology in the gross in the wet organs, and I also think it probably would be more interesting to you if we conducted this as though we were looking at some war gas casualties when we didn't have any indications as to what the animals died of. For that reason I have brought another dog down besides this one, and I have already mentioned that this dog was gassed with one type of gas and this with another.

I have chosen a gas from each of the two main types, the asphyxial group of phosgene and the other from the mustard group, the vesicant group, and I want to demonstrate the main pathological features of those cases.

Now, I don't know if you will ever be called upon to do an autopsy to determine the cause of death, but I hope this may give you a little picture of what it means. On the charts we see that phosgene causes pulmonary edema with very little damage to the upper respiratory tract, while the vesicants show destructive lesions in the upper respiratory tract and the nasopharyngeal region and tracheal mucous membrane, and then in addition some edema and production of bronchial pneumonia and also the systemic actions.

In any autopsy, of course, the information that we seek is what is the causative agent or the cause of death. Of course, the first thing noticed as you look at this dog is the foam coming from the animal's nose. That, of course, practically gives the question at hand away. An examination of the eyes reveals that the eyes are those of a normal dog. On opening the mouth the pharynx contains a pool of red stained fluid. This dog has some superficial lesions over the toes which might be confused with mustard burns. Of course, we have to look for mange in this type of animal. On the slides that I will show you I will try to demonstrate the histology and the gross material.

One of the things that we see at this stage of the autopsy is that the tissues surrounding the trachea and larynx are not hyperemic, that is, not engorged with blood, and there is no vaso-dilatation. If I occasionally slip and explain terms which you all know, please forgive me, because I have been

giving some of these lectures to people who don't know what a red blood cell is.

Now, those of you who can see the lungs in situ here see that they almost completely fill the chest cavity. When the chest cavity is opened and the negative pressure released, they do not collapse, showing that there must be something in them.

Now we will make a slit in the trachea and see the source of the froth which we saw coming from the nose and which was in the back of the pharynx. (The trachea is filled with fluid and froth) I will take these lungs out. These lungs demonstrate as well as you will ever see it the typical picture of lungs in phosgene poisoning. Over the surface of the lungs you see that the lung is mottled and those areas appear to you as a light pink and a deep red. You notice on close inspection of the lung that the light pink areas are raised from the surface while the dark areas are rather flattened. Now, the light pink areas are little focal points of the emphysema that the air has been trapped in by the rapidly forming edema. In the other areas the alveoli are practically collapsed and in sections you see them almost completely filled with edema fluid. In some of these areas, typically in animals that lie so that one lobe is lowered so that the edemal fluid has a hard time getting out and drainage is difficult in those areas, frequently the edema fluid coagulates and becomes consolidated; where the edema fluid changes from a water-like fluid, or pure transudate, to an exudate containing cells, you get the picture of acute bronchial pneumonia.

The other thing you would see at the autopsy table would be that the lungs of this dog would be greatly increased in weight, the lung weight - body ratio would be away up.

Now, in these animals gassed with phosgene examination of the other viscera usually reveals very little pathology. One point brought out here was whether or not the right heart was dilated. From my experience and the experience of quite a few others, the right heart is frequently dilated. In the heart before us the right chamber appears to be dilated, forming a cleft at the apex, but interestingly enough, when blood pressures are taken of the venous circulation, there is no rise reported.

Perhaps the terminal thing is a right heart failure.

The other viscera are usually not remarkable. The spleen of this dog is of normal appearance and normal size, the kidneys normal. They sometimes show cloudy swelling, but this one does not. And the liver is usually normal, but sometimes showing passive congestion. In this dog I would say it did not.

The first difference from the other dog you will note is the absence of that edema froth pouring from the animal's nose. The eyes of this animal (the corneas) show a diffuse clouding, and the conjunctiva are a dark red purplish color. Some of you who have not seen these eye changes in the gross that are caused by the nitrogen mustard should take particular pains to see this because in small concentrations this would be the lesion that you would be asked to treat.

Now, the inside of the mouth of this dog, in contrast to the other dog, does not contain edema fluid, and you will notice that the skin of the mucous membrane inside the mouth is hyperemic, it is inflamed, and down in the posterior part of the pharynx there is some mucous. The redness of the skin here in the groin is a

natural hyperemia which is due to the fact that the animal is dead. In dogs, that have so much fur on them, the place where they usually are burned is in the groin, which becomes edematous and goes into cellulitis.

QUESTION: Any danger of getting mustard on your hands from the dogs that you are using there?

DR. LUSHBAUGH: Not at this time. This dog, in contrast to the other dog, was gassed five days ago. In that time I think there is not much chance of mustard staying around.

QUESTION: Did that dog die spontaneously or was it killed?

DR. LUSHBAUGH: This dog died spontaneously. Both of them did.

The other dog did not show any injection of the vessels around the trachea and showed no peritracheal hyperemia, but the vessels around the trachea of this dog are quite prominent and stand up pretty well.

QUESTION: What concentration of gas was used on this dog?

DR. LUSHBAUGH: It was approximately two tenths milligrams of nitrogen mustard per liter for ten minutes and the other was fifty-four hundredths milligrams of nitrogen mustard per liter for twenty minutes.

The thing I forgot to make a special point of with the other dog was that after the edemal fluid had been scraped away from the trachea there was no actual destruction of the trachea and mucoaa. In this dog it would not be hard at all to scrape the tracheal mucosa right away from the tracheal cartilages. I will do that for you.

In opening the trachea, the first thing you see is destruction of the mucosa, which is covered by mucous and serous fluid. The trachea is thickened, and when the larynx is cut open you see that the vocal chords are markedly edematous and there is edema and hyperemia of the glottis and small ulcerations in the larynx itself.

Now, on opening the chest cavity of this animal, the contents are different from the other animal. The pathological changes are not so much bilateral as they were in the phosgene gassed animal. There is a slight pleural effusion. The lung which does not collapse in this animal is the right lung. Of course, these pathological changes will vary from animal to animal, but from what I can see of the left lung it looks grossly normal. Now, that, of course, may indicate that the animal was lying on its right side most of the time after gassing. The heart of this animal does not show the same marked distention of the right chamber. I will just take this lung out before you come up here.

Now if you will step up here, you can see better.

I have been asked several times why don't I wear rubber gloves, and one of the questions was would I wear rubber gloves in the field if I were doing mustard casualties, and my answer is that one actually would not dare to wear rubber gloves. The only thing you can do is to keep your hands wet because, as they have learned in the munitions factories and the like where they are making mustard, mustard is very soluble in rubber. Thus the mustard would be held right against the skin. Workers with mustard who have taken their rubber

gloves off have taken the back of their hand with it. So it is much safer to hydrolize the mustard yourself with a little water than it is to protect yourself from a few germs with rubber gloves.

Now, I will pass this around, and if anyone wants to see it at their leisure they may.

Now, the other point of departure of the vesicant gases from the asphyxial gases is their effect on the other parts of the body. This animal has cloudy corneas and conjunctivitis, upper respiratory effects as well as respiratory effects, and besides that, on histological examination, you see other systemic effects. This is actually not mustard that I am showing you today, but it is the new nitrogen mustard which has been released for the first time, and it acts, as you see, very similarly to mustard.

One of the changes that we will expect to see in this type would be bone marrow damage. Actually I can't tell very much about this in the gross, but the way the bone marrow damage usually shows up is that the bone marrow, instead of being a nice opalescent red shows up as a sort of a red jelly and it is very shiny and on histological inspection you see that most of the bone marrow spaces are now filled with edema fluid and actual hemorrhage, and that the actual blood cells and blood forming cells have been lost.

Now, the spleen of the other dog you saw was a large red-purple organ. This dog, which has more infection and more local damage than the other dog, should have what we call a splenic tumor or a septic spleen. Actually it doesn't have one, but has an atrophied spleen, and that brings out another action of these gases. The lymphocytes and the spleenic follicles are injured and wiped out in large amounts and the spleenic tissue is destroyed and the spleen instead of becoming active and doing something towards the whole animal's good actually atrophies, and the same is the case with the other lymphoid organs, the thymus and lymph nodes.

Coupled with this when you follow the blood of these animals hematologically, you would find that within 12 hours after exposure to the gas there would be a rapid fall in the absolute number of lymphocytes, and a rise in granulocytes. The actual number of lymphocytes actually falls from 3 to 4 thousand down to 500 per cubic millimeter and holds that level throughout the course. During the next 48 hours the granulocytes rapidly fall until we get a reverse in the leukocyte-lymphocyte ratio and you have an apparent lymphocytosis, but in actual number you have only 5 or 6 hundred lymphocytes present, and but 40-50 granulocytes.

I have a few slides to show. This shows the lungs of a goat that was gassed with mustard, and it shows somewhat the same effect you saw in the lungs that are going around now, the spotty damage to the lungs. Here are areas which are relatively uniform and which appear emphysematous and here are two points which probably show an aspiration pneumonia, and here are atelectasis and areas filled with edema fluid.

The next slide. These are some of the common results of mustard gas. Probably some of you have seen this several times. It is from Winternitz's book, showing the destruction of the upper trachea from mustard gas erosion, soft puckered erosion throughout the trachea, and then the eyes of two dogs which actually show ulceration.

The next section. This is a typical picture of the tracheo-bronchitis which occurs after mustard gassing. Besides degeneration of the epithelium, which appears to be sloughing, there is exudation, seeping, and lymphocyte infiltration into the submucosa.

The next is a lower power view of the trachea below the larynx of a mouse gassed with mustard, showing here in this dark area a large submucosal abscess and here an aspirated food particle and sloughing of the epithelium.

This is the larynx of a cat gassed with a mustard-like compound showing the area of submucosal inflammation, actual ulceration, and the necrotic tissue being sloughed off from the area.

The next section is a picture of the bronchial pneumonia which develops following mustard and mustard-like compounds, and here a picture of the tracheal cast made up of sloughed off epithelium, fibrin, edemal fluid, and leukocytes, and this is the true mucosal surface right there.

The next section is of a widespread aspirative bronchial pneumonia in a cat following a mustard-like compound, showing the tracheitis, sloughing of the epithelium, and an entrapped bubble of air, edema fluid, and widespread infiltration of inflammatory cells. Actually this is the type of thing that occurs after four or five days. If you looked at the lungs of an animal that had just been gassed or which died one or two days after gassing, you would find that there would be a gradient of pathological damage from the upper respiratory tract down, so that actually the most acute damage would be to the pharynx and upper respiratory passages, then as you got to the larynx first and then down the trachea into the smaller bronchi, the damage would lessen. That is not true of phosgene. The damage there is away down deep in the lungs.

The next section is the left lung and the right lung of a mouse. This picture happens to be over-stained and that is why it so easily shows the consolidation in an aspirative bronchial pneumonia following mustard gas in a mouse. This is rather rare for a mouse, however. The mouse usually dies of systemic damage rather than of local damage.

The next section is to illustrate some of the systemic damage which occurs with mustard and mustard-like compounds. This is the normal thymus of a mouse and shows the thick lymphocyte rich cortex and the medulla, which is rich in lymphocytes and epithelial cells.

Now, the next section is the thymus of the gassed mouse 12 hours after exposure. The normal cells present are the large epithelial cells and these dark blobs are masses of chromatin which are destroyed lymphocytes and here and there these cells (the reticulo-endothelial cells) can be seen engulfing it. Two days from now this would be seen as a mass of tissue made of endothelial cells and showing a little area of lymphocytes near the center of the organ, and the organ itself would be called very atrophic.

The next slide shows the bone marrow of a normal mouse and would perhaps appear hyperplastic to one familiar with bone marrow cell types. This is the cortical bone. Here are the cells of the marrow. That photo was taken just after gassing, and this slide is the bone marrow three days after gassing. Osteocytes are still present, some reticulo-endothelial cells, and a few very immature myeloid cells are present. These cells are red cells coming from the dilated and ruptured sinuses. A stage between these two pictures is a picture which is usually seen in the larger animals, the so-called gelatinous

adema between the cells of the marrow.

The next section is a skin burn under low power. Its course in man would be to blister, but in the animals necrosis occurs without blistering. The necrotic area is outlined in here in black. That black margin is the mass of inflammatory cells which are infiltrating the area. The inflammation has actually gone down in the muscle under the skin.

QUESTION: Of what part of the body was this taken?

DR. LUSHBAUGH: Between the shoulder blades on the back of a mouse. In some animals these burns will go right down through into the muscle. This is the striated muscle of the shoulder blades.

The next section is a higher power of the same, showing the epithelium on the top which is necrotic, most of the cornified cells have been already sloughed off and the colagenous tissue no longer has the normal staining properties and is dying. Here is the dense leukocyte infiltration.

QUESTION: What animal was this?

DR. LUSHBAUGH: This is in a mouse, which has been a routine test animal in most of these burns. The trouble we have is that you can't get most of these animals to blister, so the problem of studying the vesicants experimentally is a little difficult.

QUESTION: Do you get any blisters in any animals?

DR. LUSHBAUGH: Well, by juggling things here and there the breast of a chicken can be gotten to blister and with the right treatment, lack of salt, and so on, I believe you can also get some ot er animals to blister. Routinely, the dogs, for instance, do not blister, but they will get large sloughs and diffuse cellulitis. Mice develop a picture like this which leads to a punched out hole in their skin when you put the vesicant on.

The next section is a typical picture of the phosgene-like type of gas showing the froth, edemal fluid in the trachea, the areas of consolidation, the edemal fluid containing lung, and the widespread damage, differing from the mustard lesion almost entirely. The mucosa here is practically undamaged, and only in 24 to 36 hours does it show any degeneration at all, and then the degeneration is just superficial and is rapidly repaired.

The next section is the trachea of a goat gassed with a substance like phosgene. The mucosa is still intact, a little edemal fluid is present but there is no great change. It is practically normal.

The next section is a higher power section of the lung of such an animal, showing the protein rich edemal fluid, stained pink with eosin, the edema of the perivesicular area which also occurs. Actually this is just a stage between a transudate and thick exudate, where the protein rich fluid and cells continue to come out.

The next section is again a picture of phosgene gassing in a cat, and you recognize exudate. In other animals you usually get a transudate. Here you see edema rich in protein and inflammatory cells.

The next is the same, showing a massive edema of the perivesicular connective tissue and edema throughout the lung.

The next is merely to illustrate the emphysema which sometimes occurs in these animals, especially when they are strug ling for breath. The elasticity of the lung connecting tissue is frequently lost.

The next shows what is sometimes the end result after phosgene poisoning, like that with mustard. It is an aspirative pneumonia and secondary infection. Here is a little area of pneumonia; most of this area is atelecstasis, probably from re-absorption of alveolar air. Here is a broncho-pneumonia type of leukocytic exudate.

The next shows the chronic effect of gassing. This happens to be from chlorine. This was 72 days after gassing and it shows chronic peribronchitis and subacute pneumonia.

The next section is another chronic bronchitis with big mucous plugs in the small bronchi, which makes the animal with such a picture a respiratory invalid.

I am willing to answer any questions anybody wants to ask. Dr. Freeman is going to bring down a dog just recently gassed which is in the extreme stage of prostration from phosgene gassing.

QUESTION: After the lesions of the bronchi, what is the final end stage as far as the possibility of degeneration of the epithelium is concerned? Will it develop a scar?

DR. LUSHBAUGH: Well, it will reepithelialize, but there are frequently constrictions of scars such as you saw in the one slide, distortion of that sort. But, of course, when those lesions occur and although there is finally gross distortion, .. it will finally reepithelialize. It takes a long time to heal, like a mustard burn.

DR. FREEMAN: This animal was gassed at the same time that the other phosgene dog was gassed whose autopsy findings you observed. This dog, of course, is obviously dyspnoeic and hyperemic. He has tachycardia and his lungs are in a similar condition to those of the animals whose lungs you observed. He is cyanotic and very cold. The body temperature now is probably lower than normal. X-rays of the lungs have been taken and they show the findings which are characteristic of this stage, that is, an emphysema and a consolidation.

QUESTION: Does he have pneumonia?

DR. FREEMAN: Not yet, no. He does have a massive edema with this frothy fluid that he brings forth and back and forth, and then if you try to drain that out by hanging the head in a dependent position you get maybe just a little fluid during life, and just as soon as he relaxes with death the fluid will just gush from his mouth and stream to the floor, maybe 500 cc. or even more.

QUESTION: You can't dissipate it by the tracheal catheter, can you?

DR. FREEMAN: Bronchoscopic aspiration we tried on a series of dogs at one time and found that instrumentation of this type was out of proportion to whatever benefit might be derived. There is a recent issue of the journal called "Tuberculosis" which has an article on aspirations which were carried out on goats where they had increasing mucous secretion, and on those animals they did believe that aspiration was beneficial. That is contrary to our experience with dogs.

QUESTION: What was the journal, you say?

DR. FREEMAN: "Tuberculosis." It is one of the recent issues of the journal.

QUESTION: You mean the American Review of Tuberculosis?

DR. FREEMAN: Excuse me. No, that was called "Tuberculosis." That was a paper on goats.

QUESTION: Would oxygen help any?

DR. FREEMAN: It hasn't in our experience, nor was it beneficial in Underhill's experience.

QUESTION: Did this dog have the same exposure as the one that died?

DR. FREEMAN: Yes, they were gassed together, simultaneously.

QUESTION: How long will this dog live or is he by the worst?

DR. FREEMAN: Well, from experience with about 150 dogs, 80 percent of them die with this dose within 46 hours, and generally if they do not die within 48 hours they don't die.

QUESTION: If he recovers, is he perfectly normal afterwards?

DR. FREEMAN: If you look at the lungs in four or five days or seven or eight days, in the majority of instances the lungs are very well colored. There may be little foci, little points which are discolored and which are hemolytic and you will have exudate, and in certain instances we may get a massive infection of the lungs. I have seen dogs, on the fifth day in which the whole lungs would be invaded and they would be full of water and pus.

QUESTION: There is always some residual effect?

DR. FREEMAN: In the majority of instances the residual is very small, but you may find just little wedge-shaped areas which are consolidated towards the periphery of the lungs. The arterial saturation of this dog probably would not be over 60 or 70 percent and the venous is probably about zero; that is, with the hemoconcentration this dog probably has around 70 percent.

QUESTION: The venous pressure is high?

DR. FREEMAN: Well, we haven't studied venous pressures. Those who have studied venous pressures have gotten negative results so far as the figures go. We do know that these animals have a low tolerance for intravenous fluids. At this stage they regularly can't tolerate plasma at all.

QUESTION: Has bleeding ever been tried?

DR. FREEMAN: Yes, but you only add insult to injury because you are just stealing what fluid is left.

QUESTION: How about hypertonic fluid?

DR. FREEMAN: Hypertonic fluid again would cause more permeability of the lungs. With the protein rich exudate hypertonic fluids are of no benefit, hypertonic plasma, rather concentrated.

QUESTION: Would oxygen therapy help any?

DR. FREEMAN: It didn't in Underhill's experience, nor has it in ours.

QUESTION: How about large doses of atropine before the pulmonary edema occurs?

DR. FREEMAN: That is being studied now. I am not at liberty to give you the findings. I mean the idea of an autonomic binge is a part of the picture. I think it is very feasible and that question is being worked upon. There is a certain amount of obstruction here that is apparent, and where obstruction occurs we never know. I mean the pulmonary condition, particularly obstruction, is such as to interfere with the diffusion of gas and it is mostly local, but it is true that with the majority of obstructions the increased diffusibility of helium deserves consideration as an added measure to make the exchange of air more efficient and to make it a process with less work.

Oxygen injection through the stomach, through the circulation, and by increased pressures have all been tried, I think, with no results which would indicate, at least in the present stage of our knowledge, that it is useful. You certainly can't supplement enough to promote the survival of the animal.

QUESTION: What happens if that dog is given an I. V.?

DR. FREEMAN: Well, if you give an intravenous injection of plasma, the animal would get no more good than from injecting oxygen. You would never get an accumulation of oxygen on the right side of the heart.

QUESTION: It would not absorb?

DR. FREEMAN: No, sir.

QUESTION: Would bleeding help?

DR. FREEMAN: As far as this dog is concerned, it is very difficult to get much blood out of him at this time. Bleedings earlier in

a dog in our experience are not efficacious. That is contrary, however, to Underhill's findings. He found some benefit on bleeding.

QUESTION: What about the color of the mucous membrane in these dogs? Is there gray cyanosis or blue cyanosis?

DR. FREEMAN: Well, I might as well characterize it as natural coloration of the mucous membrane, and you can see that the tongue is definitely purple, as this dog's tongue is right now. He has a little foam starting to well up in his mouth which we will wipe off. You can see his tongue is purple; it is not the normal pink color of a dog's tongue at all.

Even the first dog in our demonstration, his tongue is a much brighter color.

QUESTION: How about blood transfusions?

DR. FREEMAN: People have used that. They spread the blood out and aerated it and then returned it to the circulation, and the experiments like that have been followed with some degree of success. I don't think there have been more than a few experiments made on it. Those experiments, of course, are of some interest from a theoretical standpoint.

Of course, the question that there has always been a lot of discussion about and very little satisfaction is with regard to the question of whether or not the action of phosgene was confined to the lungs or to some other constitutional effect, whether it is a purely local effect, and, if it was a purely local effect, what the nature of the effect is; is it a chemical injury of the heart especially or is it the trigger mechanism for some effect on the circulation or for some neurogenetic factor.

QUESTION: How about the capillary permeability elsewhere in the body before marked anoxyia has taken place?

DR. FREEMAN: I don't think there is any evidence that it is more than a condition like that in the autopsy here. The muscle is very dry and there is no peripheral ethema. I don't think there is any more than just anoxyia.

QUESTION: Do these dogs take water?

DR. FREEMAN: They do in the earlier stages. No, they won't take on much water. We generally just leave water in there and they can take it as long as they want.

QUESTION: How about his blood pressure?

DR. FREEMAN: It is low now. When the anoxyia gets pretty well along and they go over to tachycardia, it isn't very long until the blood pressure goes down.

QUESTION: Has the use of high pressure oxygen chambers been tried?

DR. FREEMAN: Yes, sir.

QUESTION: What has been the effect?

DR. FREEMAN: Well, it is all off the record as far as we are concerned. Pure oxygen is in itself a pulmonary irritant and also causes central nerve system manifestations.

QUESTION: When was this dog gassed?

DR. FREEMAN: 4:20 yesterday afternoon. You see, it is only when this terminal relaxation is going on that he begins losing the fluid. He may go on this way for quite a while.

QUESTION: Is it all from the lungs? There isn't any vomiting?

DR. FREEMAN: Well, there is retching, but the fluid which he brings up will be fluid that came from the lungs and was swallowed. We sometimes find considerable quantities of frothy fluid in the stomach as well as the intestines.

QUESTION: How about large doses of paverine?

DR. FREEMAN: Paverine has been used and the evidence on that is not convincing one way or the other. There certainly is nothing so far to contra-indicate its use and there is perhaps minor evidence that it might be beneficial, but it has not been adequately established one way or the other. The same is true of atropine.

QUESTION: You said this dog has hemoconcentration now?

DR. FREEMAN: Yes.

QUESTION: When did that start?

DR. FREEMAN: This dog probably started around 10:00 o'clock last night, because by 6:00 o'clock he was down to 45 percent and by 7:00 o'clock it may have been down to 30 or 35 percent, maybe 40 percent, and then along about 10:00 o'clock it would be about normal again, and then it would go on up, it would get up to around 65 or 70 percent, and then probably descend.

QUESTION: Would changes in the plasma proteins during that period help?

DR. FREEMAN: Plasma proteins do not; it merely is a depressant.